Sleep Loss and Inflammation

Janet M. Mullington, Ph.D.[1], **Norah S. Simpson, Ph.D.**[1], **Hans K. Meier-Ewert, M.D.**[2], and **Monika Haack, Ph.D.**[1]

[1]Dept of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Ave., Boston, MA, 02215, (617) 667-0434

[2]Dept of Medicine, Div of Cardiology, Boston Medical Center, Boston University School of Medicine, Boston, MA

Abstract

Controlled, experimental studies on the effects of acute sleep loss in humans have shown that mediators of inflammation are altered by sleep loss. Elevations in these mediators have been found to occur in healthy, rigorously screened individuals undergoing experimental vigils of more than 24 hours, and have also been seen in response to various durations of sleep restricted to between 25 and 50% of a normal 8 hour sleep amount. While these altered profiles represent small changes, such sub-clinical shifts in basal inflammatory cytokines are known to be associated with the future development of metabolic syndrome disease in healthy, asymptomatic individuals. Although the mechanism of this altered inflammatory status in humans undergoing experimental sleep loss is unknown, it is likely that autonomic activation and metabolic changes play key roles.

Keywords

sleep deprivation; partial sleep deprivation; inflammation; cytokines; IL-6

The sleep response to immune challenge

Physiology research in sleep-deprived animals in the 1970s identified an "endogenous factor S", (factor S standing for, sleep-promoting factor) (1), contained in the cerebrospinal fluid of sleep deprived animals that when injected into a non-sleep deprived animal, caused that animal to fall asleep. Subsequently, this factor S was characterized as a bacterial cell wall peptidoglycan fragment known as muramyl peptide, and researchers were able to show that muramyl dipeptide was able to induce IL-1beta, and that this pyrogenic cytokine could induce sleep in non-sleep deprived animals (2). Together, these findings opened the field to the role of sleep in immune responsiveness and function. As more became known about the sleep response to infectious challenge ((2, 3); see (4), for recent comprehensive review), it became clear that IL-1 beta and TNF-alpha, primary cytokines of the inflammatory system, are involved in the central nervous system regulation of physiological sleep. Initially, Toth and colleagues found that survival from host challenge with infectious agents was associated with better sleep in rabbits (5). Subsequently, in human studies, a challenge with a purified endotoxin fragment led to alterations in sleep (6, 7), with NREM sleep and delta power

dose-dependently increased (8) and REM sleep decreased (6–8). Similarly, IL-6, injected in low doses in humans, was found to result in biphasic alteration of NREM and a decrease in REM sleep (9).

Sleep, therefore, clearly responds to challenges to the host and is affected by the activation of our bodily defense mechanisms. However, the question remains as to whether or not sleep participates in immune system regulation. There is evidence that sleep is involved in the development of immunological memory (10–13), but in addition, there are data that suggest that sleep is important for other inflammatory homeostatic functions, as well. The current review focuses on the effects of sleep loss on indices of inflammatory system activation: activation that is independent of direct stimulation of the immune system through traditionally understood pathways of infection or injury.

Experimental sleep loss activates components of the acute phase response

The acute phase response refers to the rapid and early activation of an immune cascade in response to injury or infection. This response involves the activation of toll-like receptors (TLRs), a class of pattern recognition receptors, which recognize molecular patterns of self and non-self microorganisms and may be present on the cell surface or in the endoplasmic reticulum. Ten human TLRs have been described to date (14). TLRs and receptor complexes activate the gene transcription that stimulates nuclear-factor kappa-beta (NFkB) and leads to the production of a class of proteins called inflammatory cytokines, such as IL-1beta, TNF-alpha and IL-6. How different stimuli lead to the activation of these receptors and receptor complexes, and lead to qualitatively different responses, is an area of intense investigation (see two recent review series: in Cell, beginning with an essay by Medzihov (15), and in Science, beginning with an introduction by Mueller (16).

The immune cascade in response to injury or an infectious challenge involves the activation of phagocytic white blood cells (WBCs), such as neutrophils, monocytes and macrophages. These cells in turn produce inflammatory cytokines such as IL-1beta, IL-6, TNF-alpha, which further activate the host defense system and activate the hepatic production of C-reactive protein (CRP), a biomarker that has long been used clinically as a classical acute phase response indicator. CRP is a hepatic protein, stimulated by inflammatory cytokines, particularly IL-6, and is elevated more than one hundred-fold over baseline levels during acute infection, although the exact function of CRP in the immunological response remains unclear. The WBCs, most notably the monocyte-macrophage cells, are powerful producers of proteins that regulate the acute inflammatory response. This acute phase response begins within minutes after contact with an antigen and resolves over 24–48 hours, by which time the initiation of the development of immunological memory has begun, with activation of T and B cells.

Newer to the arena of immune system and inflammatory research is the investigation of chronic inflammation, or the activation of inflammatory systems that fail to resolve completely. This incomplete resolution of the inflammatory response is of interest in light of the chronic basal elevations of inflammatory mediators seen in pain syndromes and metabolic syndrome diseases. In particular, type two diabetes and cardiovascular diseases present interesting challenges to our understanding of how the metabolic and inflammatory systems interact (17–19). Also, following the discovery that adipocytes can produce inflammatory mediators (20), it has also become apparent that inflammatory mediators can induce insulin resistance and that these are tightly coupled homeostatic systems (18, 21).

Inflammation and risk for the development of disease

Markers of inflammation have been associated with increased risk for the development of type two diabetes in the Cardiovascular Health Study (22) in non-diabetic middle aged men (23) and women (24). In addition to risk for the development of diabetes, inflammation predicts poorer prognosis in the course of the disease and subsequent complications, including cardiovascular disease (CVD), retinopathy and neuropathy (25).

Elevated leukocytes were described in patients with congestive heart failure in the 1920s (26) and in the 1970s it was noted that repeat incidence of myocardial infarct was more likely in individuals with elevated WBCs (27). This latter finding is not surprising, given that elevated WBCs would be an expected indicator of severity of tissue damage. More recently, with the introduction of high sensitivity CRP (hsCRP) assays, very low level sub-clinical levels of CRP became detectable in serum and plasma. These levels were found to be associated with future risk for the development of CVD, even in healthy, asymptomatic men (28) and women (29, 30). Baseline hsCRP levels in individuals free of illness are a very sensitive marker of future risk for the development of cardiovascular disease and the use of tertile cut-offs for low risk at <1.0mg/L, average risk as 1.0–3.0 mg/L and >3.0 mg/L as high risk has been recommended (combined recommendation of the Centers for Disease Control and the American Heart Association (31)).

HsCRP is not the only inflammatory marker of risk in CVD currently available; however, it is arguably the most clinically useful because it is relatively stable across weeks and months (32), has a long half-life of 15–19 hours (33), does not show a diurnal rhythm (34), and there is a growing body of normative data available. In addition to hsCRP, IL-6, serum amyloid-A, and in some studies, cellular adhesion molecules, have been associated with increased risk for cardiovascular disease (30, 35).

Inflammatory consequences of short term experimental sleep loss

To date, most studies have involved acute total sleep deprivation (involving no sleep from time of awakening for 24 hours and in some studies for up to 126 hours). Study designs using acute partial sleep deprivation (a single night of reduced sleep time) or chronic partial sleep deprivation (multiple nights of reduced sleep time) have also been used. Chronic partial sleep deprivation protocols typically last for 2–14 days, and attempt to model physiological effects of chronic insufficient sleep. These controlled experimental models are useful tools by which to investigate the effects of sleep loss on physiological systems in healthy individuals. To date, these approaches have typically used rigorously screened, healthy volunteers as study participants, which is a necessary preliminary step in order to begin to look at the mechanisms of how sleep loss affects physiological systems, in vivo.

Studies on the effects of sleep loss on immune function have examined WBC counts and differential cells, and studied how they changed across time under conditions of reduced or absent sleep. An early experimental study involving up to five days and nights of wakefulness, conducted in Czechoslovakia in the 1960s (36), reported increased WBCs, most notably neutrophils, in response to sleep deprivation. An increase in leukocytes has been confirmed in subsequent sleep deprivation research involving continuous wakefulness of >40h (37–41). Some studies have also found increased WBC subsets, particularly neutrophils (36, 39–41), and monocytes (37, 39, 40). Most studies have found no increase in lymphocytes in response to sleep loss. Increased WBC counts in these studies of sleep deprivation were recognized as a sign of host defense activation. Later, it was found that IL-1beta, IL-6, and TNF-alpha, are also elevated during acute sleep deprivation, although the specific mediators may vary between studies (42–48).

Studies have also examined inflammatory system changes that occur in response to controlled experimental partial sleep deprivation, or reduced sleep time in individuals who normally sleep approximately eight hours per night. In the first of these studies, Shearer and colleagues (47) found that men who were permitted to sleep only two hours twice a day, once at night and once in the afternoon, for four days showed no increase in IL-6, TNF-alpha, or TNF-alpha receptors. In another study that investigated the effects of ten days of sleep reduced to 4 hours per night, no change was found in TNF-alpha or its soluble type I receptor, although IL-6 was increased (44). In another study, two hours of sleep reduction per night for seven nights led to increased TNF-alpha in healthy men but not women, but increased IL-6 in both men and women (49). In a study of sleep restricted to 4 hours per night and centered on the mid-sleep time of habitual sleep, IL-6 and CRP were also found to be elevated (45). Another recent study provided sleep opportunity for 4h/night for five nights and found increased IL-1beta, IL-6, IL-17 and hsCRP (48).

There are a number of factors to consider when interpreting data associating insufficient or disturbed sleep with inflammation. These are particularly important when considering studies with small numbers of subjects. Specifically, there are large individual differences in basal levels of inflammation that are associated with a range of factors, even in apparently healthy individuals. Among these are: stress and activity level prior to sample blood draw, proximity to meal intake, smoking status, and adiposity and other metabolic factors (discussed further below). In addition, some studies have found circadian rhythms for cytokines such as IL-6 (50–52); these finding indicate that the timing and frequency of sampling also needs to be considered. Assays used have varied in their range of sensitivity and specificity and thus, detectability and ease of measurement may influence selection of analytes and outcomes. Effects of catheter (53) and contamination (54) may further contribute to noise in the data and cause spurious results. Given this multitude of factors, the inclusion of appropriate controls and specimen documentation are essential, as is replication and analysis of the relationship between sleep loss and inflammation from multiple study approaches.

In sum, well-known markers of the acute inflammatory system, IL-1 beta, TNF-alpha, IL-6 and CRP have all demonstrated responsiveness to sleep manipulation in humans. Many experimental factors, such as light and activity levels, experimental activities and stress involved in the protocols or testing environments, the timing of sleep loss and sampling frequency, as well as genetic and individual differences in responsiveness to stimulation by sleep loss, may underlie the pattern of cytokine stimulation seen in a given study. Alteration from basal levels indicates an activated inflammatory system. While commonly referred to as "pro-inflammatory", they are in fact pleiotropic cytokines that have receptor families that help to regulate the balance of the inflammatory response. Redundancy built into the inflammatory cytokine network such that, very often, if one cytokine is knocked out, another can fill its role. Thus, inflammatory cytokines work together to promote and subdue the inflammatory, phagocytic and coagulatory stages involved in protecting the body and maintaining immune system homeostasis. In fact, the same cytokines can sometimes be seen to work to both increase and decrease the inflammatory response (55). How these cytokine networks communicate and work together is an intensely investigated area of research. And, more and more, the genetic influences and their implications for therapeutic intervention in these systems is appreciated (56).

Mechanisms by which sleep loss leads to inflammation

When considering the relationship between inflammation and sleep loss, it is important to keep in mind that we do not have a very deep knowledge of the relative source(s) of the cytokines we are measuring in peripheral blood. Cytokines can be produced by monocytes,

macrophages, neutrophils, endothelial cells, and adipocytes, and their relative contribution to circulating levels, certainly under conditions of sleep deprivation, is unknown. An important start in the efforts to find the source of sleep loss-associated inflammation is work showing that one night of sleep restricted to four hours led to increased monocyte production of IL-6 and TNF-alpha messenger RNA (57). While monocytes are not the only source of IL-6 and TNF-alpha, they are powerful producers, and this research indicates that this is one mechanistic pathway that is activated by sleep loss.

Autonomic activation – stress and vascular indices

One hypothesis that has been proposed to explain the relationship between elevated inflammatory mediators and risk for cardiovascular disease is that vascular changes associated with increased blood pressure result in endothelial production of inflammatory mediators (58). During healthy normal sleep, blood pressure drops to its lowest point in the day, and levels of endothelial markers decrease as well (59). During experimental sleep deprivation of healthy volunteers, blood pressure and other indicators of sympathetic output have been found to increase (45, 60, 61), as have cellular adhesion molecules, which are pro-coagulatory markers produced by stimulated vascular endothelium (e.g., E-selectin and ICAM-1; (43, 62)). It has been argued that shear stresses, or physical stress forces, associated with increased blood pressure may activate inflammatory mediators (58, 62). This could occur through increased endothelial activation and production of inflammatory mediators, such as IL-6.

In terms of the relationship between vascular stimulation and inflammatory activation, Sauvet and colleagues have recently shown concomitant inflammatory and sympathetic activation and microvascular changes in response to sleep loss (46). Of interest, in this study, E-selectin (an endothelial adhesion marker) and impaired microvascular reactivity changes seen over the course of 40 hours of sleep deprivation actually preceded an increase in blood pressure, norepinephrine and IL-6. In a study of macrovascular response to occlusion using the flow-mediated dilation test of the brachial artery following over 54 hours of sleep loss, dilation – another sign of vascular stimulation - was reduced in participants who had undergone the extended vigil (63).

In addition to vascular mechanisms, it has been hypothesized that alterations in the stress response system during sleep loss may contribute to observed inflammatory changes. Plasma or saliva cortisol concentration are widely used markers of stress in human research, and in sleep deprivation studies they are usually not found to be elevated, although some studies do see elevations in the afternoon (64) or early part of the night (65)- times when cortisol is on the descending limb of its circadian rhythm or at its nadir. Blood pressure and norepinephrine are additional indicators of stress and autonomic activation and have also been found to be elevated in sleep deprivation studies. These activations of the stress response system may be even more pronounced in individuals who are already vulnerable. For example, in individuals with hypertension, even half a night of sleep deprivation elevates blood pressure the next day (66). Other types of physiological stressors have also been shown to produce elevations in stress markers, as well as inflammation. For example, in human subjects undergoing exercise stress, catecholamine elevation is associated with increased inflammatory mediators (67). Additionally, norepinephrine has been found to stimulate in vitro production of IL-6 and TNF-alpha (68, 69).

Insulin resistance

Metabolic systems are of particular interest in the discussion of possible mechanisms to account for elevated inflammatory mediators during sleep deprivation, particularly because of the contributory role of insulin resistance in the development of impaired vascular

function and increased inflammation (25). Additionally, evidence for an effect of sleep loss on glucose metabolism is mounting. For many years it was known that acute sleep deprivation leads to physiological changes consistent with slowed glucose metabolism (36, 70, 71). In 1999 data was published showing that 6 nights of sleep loss (4 h sleep/night) leads to decreased glucose tolerance, as tested by the intravenous glucose tolerance test (ivGTT;(64)). While that landmark study did not find reduced insulin sensitivity, it has recently been demonstrated in two studies. In one(72), 14 nights of sleep scheduled to 5.5 hours per night found decreased insulin sensitivity in response to the ivGTT and in another, using a euglycemic hyperinsulinemic clamp method, insulin sensitivity was reduced following seven nights with sleep opportunity reduced to 5 h per night (73). While a study with 40 healthy adults whose sleep was reduced by 1h/night failed to find an effect on glucose tolerance (74), a study involving a single night of sleep restricted to 4 hours, albeit with only 9 participants, reported increased glucose production and decreased peripheral insulin sensitivity, consistent with hepatic and peripheral effects on glucose metabolism (75). Moreover, qualitative changes in sleep may underlie the development of altered glucose metabolism, as just 3 nights of disrupted deep sleep (the phase of sleep with most slow frequency electroencephalographic activity), led to reduced insulin sensitivity without increased insulin release (76). While that study did not measure cytokines, a recent study of two nights of fragmented sleep found reductions in insulin sensitivity and glucose effectiveness (77); albeit without changes in IL-6 or hsCRP.

Whether sleep-loss associated insulin resistance itself is sufficient to cause the inflammatory changes observed during sleep deprivation is an open question but it has long been established that inflammatory processes are activated in obesity and type two diabetes (78). Elevations in WBCs at baseline were associated with development of diabetes in a longitudinal study of Pima Indians living in Arizona, who at entry to the study had normal glucose tolerance when tested with an oral glucose tolerance test (79). Insulin has been shown to induce direct stimulation of TNF-alpha (20), and other inflammatory mediators along the NFkB cell-signaling pathway also participate in inducing insulin resistance (80).

Epidemiological connections

Sleep duration and risk for all cause mortality

Several studies have shown that both short and long sleep duration are associated with negative health outcomes, as well as all-cause mortality. Two recent meta-analyses of population based studies examining the relationship between sleep duration and all cause mortality reported a 10% and 12% increased all-cause-mortality in individuals with habitual short sleep duration ((81) and (82), respectively). These same two meta-analyses found increased mortality associated with long sleep 23% and 30%, respectively. Long sleep and all-cause mortality relationships were found to be stronger in older than younger cohorts, and co-morbidities are likely to play a role in these associations. While the relationship between short sleep duration and mortality may seem modest, it translates to large numbers of deaths, worldwide. Understanding the causal pathways of these relationships will require more prospective research and sophisticated modeling methods applied to population data, and highly controlled research designed to elucidate mechanisms (83).

Obesity, inflammation and short sleep duration in population based studies

There is mounting evidence that insufficient sleep leads to obesity (reviewed elsewhere in this issue). It is also well established that increased body-mass-index and associated adiposity (particularly visceral adiposity) is associated with elevated circulating inflammatory mediators (84). These findings lead to the important question about whether there is an independent relationship between inflammatory mediators and sleep duration at

the population level? Based on a limited number of studies, the independent relationship appears relatively weak. Taheri and colleagues (85), in an analysis of 907 adults in the Wisconsin Sleep Cohort study, found no relationship between hsCRP and measures of self-reported sleep duration. To date, there are few large cohort studies examining potential relationships between sleep and inflammation, and results from these are also not conclusive. One study, including 4011 young adults who estimated their degree of sleep disturbance, found that CRP was related to self rated sleep disturbance in men but not women (86). In another cohort that included over 4600 subjects, higher CRP measures were associated with shorter sleep duration in women, but not in men (87). While these studies provide important preliminary data regarding inflammation and sleep duration in the general population, it is important to consider that in order to obtain adequate numbers all along the spectrum of sleep durations, and to be able to statistically partial out the variance attributable to confounding factors, very large cohorts are needed. As such, even larger studies will likely be required to more comprehensively understand this relationship.

An additional challenge in interpreting results from associations observed between self-reported sleep duration and inflammation or other risk indices is the accuracy of self report data. While the relationship between self-reported sleep duration and sleep duration as measured by actigraphy, for instance, is reasonable (88, 89), studies have shown that even in healthy populations subjectively estimated sleep duration may overestimate actigraphically measured sleep duration (90). Additionally, there is even less information about how self-reported estimates of sleep duration may be related to more objectively-derived measures of sleep duration in populations of individuals with sleep disorders. Other challenges for these studies include selection of time of day for blood sampling, and the fact that generally only a single sample is attainable, as well as making sure that subjects are free from acute illness when tested.

One study that included objective assessment of sleep quality and duration was conducted as a subset of the Cleveland Family study and included 614 participants age 16 years or older, who kept sleep logs and had sleep recorded by polysomnography (PSG). This overnight sleep study was followed by a fasting blood sample, and circulating levels of IL-1beta, TNF-alpha, IL-6 and hsCRP were measured. Investigators found that for each hour of reduced sleep obtained by PSG, samples measured 12% more circulating hsCRP and TNF-alpha, and 9% more IL-6 (91). Following adjustment for a number of covariates, most importantly obesity, only the associated with increased TNF-alpha remained, with an 8% increase for each hour of reduced sleep. Self-reported habitual sleep time, in contrast, showed relationships with longer sleep duration, such that for each hour of increased self-reported habitual sleep duration, CRP levels increased by 8%, IL-6 by 7% and TNF-alpha by 5% (though showed only a trend towards significance). The authors suggested that self-reported sleep duration and polysomnography measurement on a single night may be measuring differing constructs of sleep, which is a reasonable assumption. None-the-less, it appears that the inflammatory system is influenced acutely by actual sleep duration, and in the longer term, by self-estimates of habitual sleep duration. This combination of approaches was revealing in terms of dissociating the acute from chronic inflammatory response in the same population, and underscores the power of having a physiological arm in a cohort study.

If, as has been suggested by numerous studies reviewed in this issue, adiposity - and we would argue inflammation - lie along the causal path between sleep-behaviors and health outcomes, it is not surprising that these relationships are weakened by the removal of variance due to body mass index and other indices of adiposity status. What are needed are models that incorporate psychosocial and behavioral factors along their causal paths so that interventions can be optimized (83).

Future Directions

While the discussions in this paper have focused on experimental sleep loss in healthy populations and possible mechanisms of inflammation, elevations of inflammatory markers have also been reported in clinical populations of disturbed sleep, including insomnia and sleep apnea (92, 93). Furthermore, patients experiencing chronic pain frequently have elevated inflammatory mediators and impaired sleep (94). Inflammatory markers, including prostaglandins and pro-inflammatory cytokines, have been shown to sensitize nociceptors (i.e., decreasing their response threshold), thereby contributing to the development and/or amplification of spontaneous pain and hyperalgesia (95). Indeed, experimental sleep loss in healthy adults leads to generalized pain by self-report and the experience is correlated with increased prostaglandin E2 and IL-6 (44, 96), suggesting a mediating role of inflammatory markers in the connection of sleep loss and pain that needs to be explored in future research.

Finally, there is some evidence that sex, age and other demographic factors may influence individual responses to sleep deprivation (49). The need for the study of individual differences is made apparent by the fact that while most studies have found inflammatory mediators to increase (and sometimes decrease) in response to acute sleep deprivation, these studies have been primarily conducted in men (36, 37, 40, 45, 47). Few studies have investigated the inflammatory response to sleep loss in women, and sex differences have not been reported; however, the statistical power to test for sex-differences was generally lacking. In a study of men and women who underwent a week of mild sleep restriction (approximately 25% of the normal daily amount), both men and women showed increased IL-6 levels, but men also showed increases in TNF-alpha (97). Other studies have suggested that women are more responsive to the inflammatory stimulation of sleep deprivation (98, 99). For example, Irwin and colleagues showed that a single night of sleep reduced by approximately 50% resulted in activation of NF-kB in women but not men (98).

In order to develop our ability to respond to differential vulnerabilities and the need for individualized approaches to health maintenance and management of health risks with regards to sleep behavior, we need to understand individual differences with regards to sensitivity to sleep loss, in terms of autonomic, metabolic and inflammatory systems. As such, the investigation of the response to sleep loss calls for the use of a multiple systems approach. Among them, mathematical modeling that includes multiple levels of analysis and causal path approaches will help make important strides.

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Research Directions

- Understanding the relationship between short term and chronic, insufficient sleep (in quantity and/or quality), and inflammation will be an important goal of future research.

- Understanding the effects of improving sleep on inflammatory processes will also be important as we move into sleep intervention studies, where a component of treatment may be sleep extension

- Examining individual differences, from a systems physiology and genetic approach, will be important for understanding differential response to sleep loss and planning interventions.

- Improved understanding of cellular mechanisms regulating the kind of inflammation that does not result directly from injury or infection is needed in order to uncover the source(s) and cause of sleep loss-associated inflammation.

Clinical Practice Points

- Inflammatory mediators participate in the CNS regulation of sleep.

- Short-term sleep loss affects inflammatory homeostasis.

- Studies in healthy volunteers to date are limited by short duration; however, they enable the careful control of experimental factors and are useful for isolating mechanisms.

- In addition to immune response, inflammatory mediators participate in the regulation and mediation of many homeostatic functions, such as insulin sensitivity and metabolism, blood pressure and sleep.

- Basal levels of inflammatory mediators have been associated with prognosis of many diseases of great public health impact, including diabetes, coronary heart disease and heart failure.

- Sleep restriction leads to a systemic increase of the concentration of inflammatory mediators that may have prognostic significance for metabolic diseases.

- At a population level, the relationship of sleep duration and disease states is confounded by many co-morbid factors.